REMARKS

Applicants respectfully request reconsideration of the application and allowance of Claims 1-15 (the only pending claims currently under examination) in view of the amendments and remarks made herein.

Amendments

Claim 1 has been amended to state that each distinct probe on the array contains a complement variable domain at its 5' end.

Support for the amendment may be found in the specification and claims as originally filed, for example at page 8 line 16, page 10 line 13 and page 17 lines 16-19, where descriptions of probes containing complement variable domains at their 5' end may be found. As can be seen, no new matter has been added by the amendment. Entry of the above amendments is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Objection under 35 U.S.C. § 132 and rejection under 35 U.S.C. § 112, first paragraph

The Office Action states that the amendment filed September 3 2002 is objected to under 35 U.S.C. § 132 as containing new matter. The Office Action further states that claims 1-15 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonable convey to on skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This objection and this rejection are based on the assertion that the subject matter of the amended claims was not adequately described in the application as filed, and, as such, the amendment assertedly introduces new matter into the disclosure of the invention. This objection and this rejection are addressed together below.

Applicants respectfully submit that the subject matter of the amended claims was adequately described in the application as filed, and, accordingly, the amendment does not introduce new matter into the disclosure of the application.

The requirement for written description involves the question of whether the subject matter of a claim conforms to the disclosure of an application as filed. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed."[1]. The MPEP § 2163.02 states that the subject matter of the claim need not be described literally (i.e. using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. Furthermore, the mere inclusion of dictionary or art recognized definitions known at the time of filing would not be considered new matter (MPEP 2163.07(I)). An application may also incorporate the content of another document or part thereof by reference to the document in the text of the specification (MPEP 2163.07(b)).

The phrase that is at issue in this object and rejection is "a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence". Since a primer extension reaction that produces a mixture of nucleic acids is an element that was present prior to the amendment, the issue at question is whether or not a primer extension reaction that produces *a solution phase* product comprising a mixture of nucleic acids of differing sequence is adequately described in the specification as filed. In other words, would one of skill in the art determine that the specification supports a *solution phase* of nucleic acids of differing sequence? As will be detailed below, Applicants respectfully submit that, upon reading the specification, one of skill in the art would find more than adequate support for a solution phrase of nucleic acids of differing sequences.

Beginning at page 10, line 25 of the specification, the primer extension reactions of the subject methods are described. Three different representative primer extension reactions are discussed, i.e., linear PCR, strand displacement amplification and in vitro transcription. Common to each of these methods is the use of primer extension as a step in the subject methods. As is clear to those of skill in the art, each of these different representative methods produces a product that is in solution phase, as further described in the subsequent pages.

Furthermore, primer extension reaction that produces a solution phase product mixture of nucleic acids is described in detail on page 18 lines 2-5 of the specification, where a 250μl reaction (i.e., a primer extension reaction of a liquid volume of 250 micro-liters) is described. Also, step 4 of the detailed methods outlined on page 18 lines 11-13 of the instant specification recites a step where products of a primer extension reaction are removed from experimental samples and directly concentrated over 10-fold by a Microcon-3 ultrafiltration

[1] In re Gosteli, 872 F.2d 1008, 1012

concentrator. As is known in the art, Microcon-3 ultrafiltration concentrators are used for concentrating liquid samples (they cannot be used to concentrate solids, gasses or plasma -the other three states of matter). As such, one of skill in the art would recognize that the products of the primer extension reaction exemplified in this section of the application are in liquid solution, otherwise they could not be concentrated by a Microcon-3 ultrafiltration concentrator. Accordingly, one of skill in the art would find support for a solution (i.e. a liquid) containing the products of the primer extension reaction, as recited in the claims.

Based on the foregoing, the Applicants respectfully submit that one of skill in the art would unequivocally find adequate description of "a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence" in the application as originally filed. Accordingly, the phrase "a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence" cannot represent new matter.

Since the phrase "a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence" does not represent new matter, the objection to the amendment filed September 3, 2002, under 35 U.S.C. § 132 and the rejection of claims 1-15 under 35 U.S.C. § 112, first paragraph, may be withdrawn.

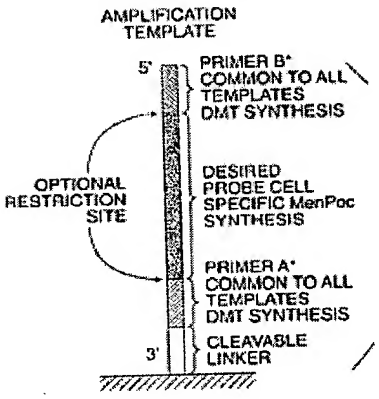
Rejection of claims 1-4 under 35 U.S.C. § 102

Claims 1-4 are rejected under 35 U.S.C. § 102(e) as anticipated by Lipshutz (USPN 6,280,950), assertedly because Lipshutz describes a primer extension reaction performed upon an array of nucleic acid probes that assertedly anticipates the instant claims.

Claim 1 has been amended to recite an array of distinct single-stranded nucleic acid probes where each distinct probe present on the array contains a a complement variable domain at its 5' end. In other words, Claim 1 recites an array containing probes that have variable domains at their 5' ends. As such, in order to anticipate Claim 1, or any claim dependent therefrom, an anticipatory reference must disclose an array containing probes that have variable domain at their 5' ends.

Lipshutz discloses a method for producing a mixture of nucleic acids involving an array of nucleic acid probes. The composition of Lipshutz probes is described in great detail in column 2 line 66 to column 3 line 35 and summarized in the first panel of Fig. 1 of the Lipshutz disclosure. This panel of Fig. 1 of the Lipshutz reproduced here for the Examiner's convenience.

First panel of Figure 1 of Lipshutz (USPN 6,280,950):



As can be seen from the figure, the Lipshutz probes contain regions at the 5' and 3' ends of the probes that are called "PRIMER B* COMMON TO ALL TEMPLATE DMT SYNTHESIS" and "PRIMER A* COMMON TO ALL TEMPLATE DMT SYNTHESIS", respectively. These regions are homologous to the constant regions of the probes recited in the instant claims. These probes are the only probes on Lipshutz' array, and, as such, Lipshutz only teaches an array containing probes containing constant regions at their 5' ends.

Accordingly, Lipshutz cannot anticipate claims 1-4, which require an array containing polynucleotides that have variable domains at their 5' ends.

Furthermore, one of skill in the art would not be motivated to modify the Lipshutz array to contain probes that have variable domains at their 5' ends since all of Lipshutz primer extension methods involve amplification reactions that require the presence of two constant domains as primer sites (e.g. non-linear PCR amplification). A variable domain placed on the 5' end of Lipshutz probes would not be amplifiable using Lipshutz' methods, and, as such, one of skill in the art would motivation to change Lipshutz' methods to teach the claimed method.

Because the Lipshutz fails to teach an array containing probes that have constant domains at their 5' ends, Claims 1-4 are not anticipated by Lipshutz and this rejection may be withdrawn.

Rejection of claims 5, 6, 8 and 9 under 35 U.S.C. § 103

Claims 5-9 are rejected under 35 U.S.C. § 103 as being obvious over Lipshutz.

With regard to obviousness, §1242 of the M.P.E.P. teaches at that:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, whether in the

> references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

In other words, in order to establish a *prima facie* case of obviousness, all of the claim limitations must be taught or suggested by a reference or combination of references. Furthermore, it is well established that a *prima facie* case of obviousness can be rebutted when the references actually teach away from the claimed invention.[2]

Thus, if the art teaches away from the claimed invention, a *prima facie* case of obviousness cannot be made.

The following analysis demonstrates that not only does the claimed invention possess elements not taught or suggested by the combination of Lipshutz, but that Lipshutz teaches away from the claimed invention. As such, the claimed invention is not obvious over Lipshutz.

Claims 5, 6, 8 and 9 require an array of nucleic acid probes that are described by the formula: surface-L-R-F-cV-5', wherein "cV" is a complement variable domain, and "5'", as is well understood in the molecular biology arts, is the 5' end of the probe. In other words, the subject matter of claims 5-9 involves an array containing probes that have a variable domains at their 5' ends. As such, in order to render the subject matter of claims 5-9 as obvious, a reference must disclose or make obvious an array containing probes containing variable domains at their 5' ends.

As established above, Lipshutz is deficient in that it fails to disclose an array containing polynucleotides that have variable domains at their 5' ends. Since this deficiency cannot be met by the knowledge of one of skill in the art, the reference fails to teach an element of the claims.

Furthermore, as discussed above, one of skill in the art would find no motivation to use probes that have variable domains at their 5' ends in Lipshutz' primer extension methods since Lipshutz' primer extension methods involve amplification reactions that require the presence of two constant domains to act as primer sites. An array of probes containing variable domains at their 5' ends would not be amplifiable using the methods of Lipshutz. As such, one of skill in the art would find no motivation and indeed would be strongly led away

---

[2] *In re Geisler*, 116 F.3d at 1469, 43 U.S.P.Q.2d at 1346

from, using Lipshutz' methods with an array of probes containing variable domains at their 5' ends.

In summary, Lipshutz fails to teach a required element of Claims 5, 6, 8 and 9 and, as a point of fact, strongly teaches away from the required element. As such, Lipshutz cannot make the subject matter of Claims 5, 6, 8 and 9 obvious. Accordingly, this rejection may be withdrawn.

Rejection of claim 7 under 35 U.S.C. § 103

Claim 7 has been rejected under 35 U.S.C. § 103(a) as being obvious over Lipshutz in view of Dattagupta, assertedly because Lipshutz' method for producing a mixture of nucleic acids, in combination with Dattagupta's RNA polymerase, render the claims obvious to one skill in the art. Applicants respectfully traverse the rejection.

Claim 7 is dependent on Claim 5, and, as such, is limited to methods that involve an array of probes containing variable domains at their 5' ends.

As established above, Lipshutz is deficient in that it does not teach an array of probes containing variable domains at their 5' ends. This deficiency is not made up by Dattagupta's RNA polymerase, and cannot be met by knowledge available to one of skill in the art, especially in view of Lipshutz teaching away from using such probes. As such, the combination of Lipshutz and Dattagupta cannot render the subject matter of Claim 7 obvious. Accordingly, this rejection may be withdrawn.

Rejection of claims 10-15 under 35 U.S.C. § 103

Claims 10-15 have been rejected under 35 U.S.C. § 103(a) as being obvious over Lipshutz' in view of Cantor, assertedly because Lipshutz' method for producing a mixture of nucleic acids, in combination with Cantor's methods of employing the mixture of nucleic acids to duplicate template arrays, renders the claims as obvious.

Each of Claims 10-15 involves the method of producing a mixture of nucleic acids recited in Claim1. As such, each of Claim 10-15 involves an array containing probes having variable domains at their 5' ends. Claims 10-13 further involve a target generation step in which target nucleic acids are produced from an mRNA sample. The target generation step requires a variable domain at the 5' end of the probes for a target to be generated.

As established above, Lipshutz is deficient in that it fails to disclose an array containing probes that have variable domains at their 5' ends. As further established above,

Lipshutz strongly teaches away from using probes that have a variable domain at their 5' ends since Lipshutz' primer extension methods involve amplification reactions that require the presence of two constant domains acting as primer sites.

Cantor's methods of employing Lipshutz' mixture of nucleic acids fails to meet Lipshutz' deficiency. As such, Lipshutz in combination with Cantor fails to teach the claimed invention.

Further, the Lipshutz method involves probes with constant domains flanking a variable domain. If Lipshutz was combined with Cantor, the combined methods could not be used in the target generation step since this step requires probes containing variable domains at the 5' ends. One of skill in the art would again be strongly pointed away from combining these references because it would result in an inoperable combination.

Since the above deficiency cannot be met by one of skill in the art, especially in light of Lipshutz' teaching away from meeting this deficiency, Lipshutz in view of Cantor cannot render the claims as obvious.

As such, Lipshutz in view of Dattagupta cannot render the subject matter of Claim 7 obvious. Accordingly, this rejection may be withdrawn.

CONCLUSION

The applicant respectfully submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Gordon Stewart at 650 485 2386. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,

Date: 2.3.03

By: _____
Bret E. Field
Registration No. 37,620

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice Amended) A method for producing a mixture of nucleic acids, said method comprising:

(a) providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on said array comprises a constant domain and a complement variable domain, wherein said complement variable domain is at the 5' end of said each distinct probe;

(b) hybridizing nucleic acids complementary to said constant domain with said array of single-stranded probe nucleic acids to produce a template array of overhang comprising duplex nucleic acids, wherein each overhang comprising duplex nucleic acid of said array comprises a double-stranded constant region and a single-stranded variable region overhang;

(c) subjecting said template array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence; and

(d) separating said mixture of nucleic acids from said template array.